

## RESEARCH LETTER

## Fatigue, Cardiovascular Decline, and Events after Breast Cancer Treatment



### Rationale and Design of UPBEAT Study

Although survival rates for stage I to III breast cancer have greatly increased, in part due to improved treatment options, this progress is threatened by increased cardiovascular (CV) events for survivors. More than 35% of women experience CV injury, left ventricular (LV) dysfunction, exercise intolerance, and/or fatigue after receipt of neoadjuvant or adjuvant chemotherapy for stage I to III breast cancer (1,2). There are, however, major gaps in scientific knowledge regarding the origins and causes of increased CV dysfunction, exercise intolerance, and fatigue in this population.

The UPBEAT (Understanding and Predicting Fatigue, Cardiovascular Decline, and Events After Breast Cancer) study will prospectively determine the influence of neoadjuvant and adjuvant chemotherapy on the following: 1) CV and physical function; 2) submaximal and maximal exercise capacity; 3) fatigue; and 4) future CV events in a cohort of 1,000 women (840 with stage I to III breast cancer and 160 healthy control participants). This study ascertains pre-existing and dynamic changes during and after chemotherapy receipt with active surveillance of subsequent CV events for 7 to 10 years following treatment. UPBEAT is designed to address these knowledge gaps by prospectively identifying which baseline and early dynamic changes may precede CV dysfunction and exercise intolerance (Figure 1).

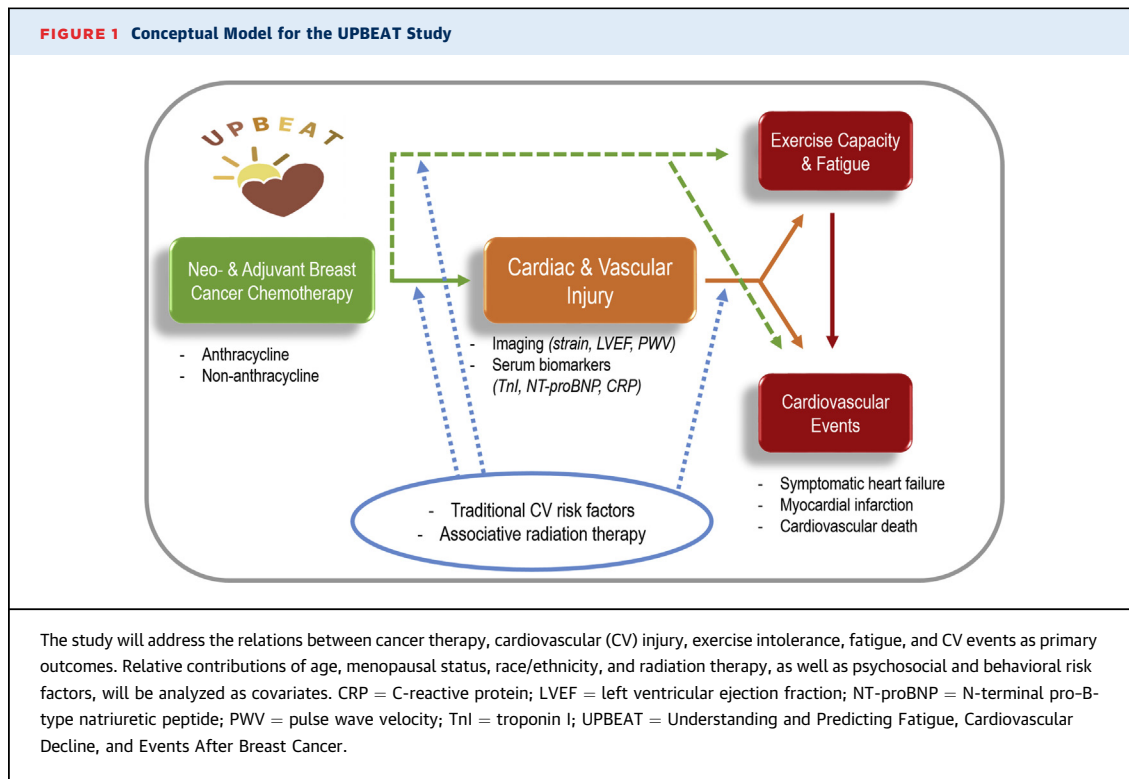
The UPBEAT study is currently recruiting participants through academic and community-based medical centers who are affiliated with either the Wake Forest NCI Community Oncology Research Program (NCORP) or the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN)/ECOG-ACRIN NCORP. Currently, 239 participants have been enrolled (127 in the breast cancer group; 112 control subjects) across 12 centers.

Participants receive a laminated schedule card of visits and monthly motivational text messages to promote retention as well as the following incentives: an UPBEAT tote bag, honoree stickers for study visits, and gift cards at each study visit. This plan has resulted in 94% retention (in both groups) at the 3-month visit. UPBEAT is a highly collaborative study, and welcomes those interested in participating as a study site or submitting an ancillary study proposal to contact the corresponding author.

All patients meeting eligibility criteria at participating sites are invited to enroll and may identify family or friends as healthy control subjects; participating sites may also locally recruit through flyers. Baseline for control subjects is considered to be time of consent and study enrollment.

Inclusion criteria common between the groups include: age 18 years or older; ability to hold breath for 10 s; ability to walk at least 2 blocks without chest pain, dyspnea, or syncope; and ability to exercise on a treadmill or stationary cycle. For participation in the chemotherapy group, women must have stage I to III breast cancer (including inflammatory, newly diagnosed, or locally recurrent being treated with curative intent but not metastatic breast cancer), be scheduled to receive chemotherapy, and have an ECOG performance status of 0 to 2. Patients may also participate in other ongoing clinical trials. Women in the control group must be healthy; have no history of cancer or breast surgery; have no previous exposure to chemotherapy, radiation therapy, or immunotherapy; and have an ECOG performance status of 0 to 1.

Exclusion criteria include inability to provide informed consent, contraindications to cardiovascular magnetic resonance (CMR) imaging, a known LV ejection fraction (LVEF) <50%, pregnant or breastfeeding at baseline, severe pulmonary hypertension, history of either acute pulmonary embolus or deep vein thrombosis within 6 months, or any history of the following conditions within the past 1 month: myocardial infarction, unstable or stable angina, left main coronary artery disease, symptomatic heart failure, uncontrolled hypertension, severe valvular heart disease, uncontrolled metabolic disease, aortic aneurysm or dissection, uncontrolled arrhythmia causing symptoms or hemodynamic compromise, or



hypertrophic obstructive cardiomyopathy. Additional control group exclusion criteria include inflammatory conditions and known coronary artery disease or heart failure. Because the healthy control group may lack representation of common CV risk factors, this selection bias may limit generalizability. To address this limitation, UPBEAT has a data-sharing agreement with the MESA (Multi-Ethnic Study of Atherosclerosis) to explore data in a more generalizable control group.

The primary endpoints include a 6% LVEF decline or LVEF <50% (2) and aortic pulse wave velocity. These primary outcomes are acquired with a 10- to 15-min rapid CMR examination at baseline, 3 months, and 24 months (Figure 2). CMR is the gold standard for volumetric quantification; it measures cardiac and vascular structure and function, and does not use ionizing radiation.


The secondary CMR outcomes include LV end-diastolic and end-systolic volumes and mass (3), myocardial strain and strain rate, mid-cavity short-axis LV myocardial T1 and T2 (4), and abdominal body composition measures. The primary exercise performance measure is the 6-min walk distance to measure submaximal exercise capacity, an independent predictor of CV mortality (5). Peak oxygen consumption,

measured at a subset of sites, is the secondary exercise capacity outcome because it is an objective measure of maximal exercise capacity, integrates the physiological response to exercise, and provides exercise and exertional fatigue data (6).

Fatigue and health-related quality of life (HRQOL) questionnaires and both cognitive and physical function measures are collected. Fatigue is measured by using the Functional Assessment of Cancer Therapy-Fatigue scale that assesses fatigue and anemia-related concerns in people with cancer. HRQOL and health status are measured by using the RAND 36-item Short Form Health Survey to assess general HRQOL and the shortened Kansas City Cardiomyopathy Questionnaire to assess physical limitations, symptoms, HRQOL, and social limitations. Cognitive function is assessed with a Controlled Oral Word Association test, the Trail Making A & B cognitive test, and self-reported cognitive function questionnaire. Physical function is assessed with the Short Physical Performance Battery protocol, grip strength, and upper body range of motion.

In addition, the following psychosocial and behavioral covariates (which also affect fatigue and exercise intolerance in breast cancer survivors) are assessed: depressive symptoms, assessed by using

**FIGURE 2 UPBEAT Study Measures**

 <b>UPBEAT Study Measures</b>	
<b>Vitals / Demographics<sup>1</sup> – BL, 1M, 3M, 12M, 24M</b> <b>Routine Labs – BL, 1M, 3M, 12M, 24M</b> <i>Lipid panel</i> <i>Serum creatinine</i> <i>C-reactive protein</i> <i>Glucose</i> <b>Stored Serum, Plasma – BL, 1M, 3M, 24M</b> <b>DNA – BL, 1M</b> <b>Questionnaires – Outcomes – BL, 3M, 12M, 24M</b> <i>Cognition<sup>2</sup></i> <i>Fatigue<sup>3</sup></i> <i>Health-related quality of life<sup>4</sup></i> <b>Neurocognitive Testing – BL, 3M, 12M, 24M</b> <i>COWA<sup>5</sup></i> <i>Trail Making A &amp; B</i> <b>Physical Function – BL, 3M, 12M, 24M</b> <i>Grip strength</i> <i>Range of motion</i> <i>Short Physical Performance Battery</i>	<b>Exercise Testing – BL, 3M, 12M, 24M</b> <i>Sub-maximal: 6 min walk distance</i> <i>Maximal: CPET – Peak VO<sub>2</sub><sup>6</sup> (BL and 24M only)</i> <b>Questionnaires – Covariates or Risk Factors – BL, 3M, 12M, 24M</b> <i>Depression<sup>7</sup></i> <i>Hostility<sup>8</sup></i> <i>Perceived stress<sup>9</sup></i> <i>Physical activity<sup>10</sup></i> <i>Sleep disturbance<sup>11</sup></i> <i>Social support<sup>12</sup></i> <i>Walking self-efficacy</i> <b>Rapid Cardiac MRI ( &lt; 15 min protocol ) – BL, 3M (cancer only), 24M</b> <i>LV volumes and mass, LV ejection fraction</i> <i>LV strain and strain rate</i> <i>Aortic pulse wave velocity</i> <i>Aortic distensibility</i> <i>T1 and T2 maps</i> <i>Abdominal body composition</i> <b>Active Outcomes Surveillance (7-10 years)</b>
<small><sup>1</sup>Vitals and demographics include heart rate, blood pressure, height, weight, body mass index, and waist circumference; <sup>2</sup>Applied Cognition – Abilities, and Applied cognition- General Concerns questionnaire; <sup>3</sup>FACT-fatigue = Functional Assessment of Chronic Illness Therapy Fatigue scale; <sup>4</sup>Kansas City Cardiomyopathy (KCCQ-12) questionnaire and Rand MOS 36-item Short Form Health (SF-36) survey; <sup>5</sup>Controlled Oral Word Association (COWA) test; <sup>6</sup>Cardiopulmonary Exercise Testing (CPET -bike or treadmill); <sup>7</sup>Center for Epidemiological Studies Depression (CESD) scale; <sup>8</sup>Cook Medley Hostility scale; <sup>9</sup>Cohen's Perceived Stress Scale (PSS); <sup>10</sup>Patient-centered Assessment and Counseling for Exercise (PACE) sedentary behaviors scale and Godin Leisure-Time Exercise (LTEQ) questionnaire; <sup>11</sup>Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance questionnaire; <sup>12</sup>RAND Medical Outcomes Study (MOS) Social Support survey; Measures are collected at baseline (BL), 1 month (1M), 3 months (3M), 12 months (12M), and/or 24 months (24M) after enrollment.</small>	

Serial UPBEAT study measures through 24 months of observation encompass a range of cardiovascular and psychosocial measures of fatigue and exercise intolerance in breast cancer patients and healthy control subjects with up to 10 years of active annual surveillance for CV events. Abbreviations as in [Figure 1](#).

the Center for Epidemiological Studies Depression Scale; perceived stress as measured by using the Perceived Stress Scale; sleep disturbance, assessed by using the PROMIS (Patient-Reported Outcomes Measurement Information System) scale; social support, measured by using the RAND Social Support Scale to assess social, emotional, tangible information and appraisal support; walking self-efficacy as measured according to a self-efficacy scale; the PACE (Patient-Centered Assessment and Counseling for Exercise) questionnaire to assess sedentary behaviors; and the Godin Leisure-Time Exercise Questionnaire to assess self-reported physical activity.

Finally, adjudicated CV events include myocardial infarction or cardiac death (death in the presence of acute myocardial infarction, significant cardiac arrhythmia, or refractory heart failure) (7). UPBEAT also identifies symptomatic heart failure warranting hospitalization, all-cause mortality, and coronary artery revascularization (7).

Age, race/ethnicity, performance status, pregnancy status, menopausal status, and hostility are collected for each participant at study enrollment. Serial assessments of weight, height, body mass index, blood pressure, heart rate, health and family history, CV comorbidities (hypertension, diabetes, hypercholesterolemia, and coronary artery disease), smoking and tobacco use, and medications occur at study visits. Serum and plasma biomarkers (i.e., hematocrit, glucose, creatinine, low- and high-density lipoprotein cholesterol, triglycerides, total cholesterol, C-reactive protein, troponin I, N-terminal pro-B-type natriuretic peptide) are ascertained in control subjects and participants with cancer at the study visits.

Cancer diagnosis and treatment information are collected in participants with breast cancer; this information includes cancer diagnosis/staging, hormone receptor and Her2 status, and current cancer treatment (e.g., chemotherapy, surgery, radiation

therapy planning records/images, radiation dose). UPBEAT also collects information regarding hereditary gene mutations, LVEF at diagnosis, and prior primary cancer diagnosis/treatment, if available.

The sample size of 840 breast cancer patients and 160 healthy participants was chosen to address the specific aims for between-group (healthy participants vs. healthy participants) and within-cancer-group (anthracycline vs. non-anthracycline) comparisons (assuming 85% retention rate) to identify a detectable difference for a measure assuming a correlation between repeated measures of 0.50, 90% power, and  $\alpha = 0.025$  (given 2 primary outcomes). For binary outcomes, there is  $\geq 90\%$  power to detect a 9% difference between groups and an 8% difference in within-group comparisons assuming that 10% in the non-anthracycline group have this outcome and  $\geq 18\%$  of anthracycline-treated patients have this outcome.

Longitudinal mixed models will be used to compare both continuous and binary outcomes, which accounts for the repeated assessments of the patients in modeling and will include fixed effects for group (e.g., anthracycline-treated breast cancer patients, non-anthracycline-treated breast cancer patients, healthy participants), baseline assessment of the outcome of interest (e.g., LVEF, pulse wave velocity, fatigue), and the time point at which the measurements are made relative to the baseline pre-CMR imaging assessment. Additional patient-level risk factors will also be considered as fixed effects in this model. Of primary interest in many of our hypotheses will be the main effect terms for group and the group  $\times$  time interaction terms. In addition, we will examine in sequential models whether cardiac or vascular measures mediate the association between groups and outcomes. Some women may not complete the study, leading to missing data. We will compare the baseline characteristics of participants who drop out versus those who do not to determine if missingness is noninformative, and analyses can be performed by using the proposed repeated measures mixed models adjusted with these covariates. However, if evidence exists that the missing data are informative, an analysis using more sophisticated statistical methods such as multiple imputation will be applied.

To the best of our knowledge, this is the first prospective cohort study designed to fully characterize the time course and correlates of subclinical CV dysfunction, exercise intolerance, fatigue, and CV events in women treated with chemotherapy for breast cancer. The immediate impact of this

cardio-oncology research will reduce the knowledge gaps surrounding CV health of breast cancer survivors through a well-characterized cohort study. In a study of this magnitude, it is important to assess a wide range of measures to understand pre-existing risk factors and dynamic changes associated with chemotherapy for breast cancer that increase risk for CV damage. The UPBEAT study may also influence future monitoring of subclinical CV disease in cancer treatment trials, identify potential mechanisms, and inform cardio-oncology study development to reduce CV disease and improve overall survival and quality of life in women with breast cancer.

Jennifer H. Jordan, PhD, MS

Ralph B. D'Agostino, Jr., PhD

Nancy E. Avis, PhD

Shannon L. Mihalko, PhD

Peter H. Brubaker, PhD

Dalane Kitzman, MD

Karen M. Winkfield, MD, PhD

Cynthia K. Suerkin, MS

Kerryn W. Reding, PhD, MPH, RN

Heidi D. Klepin, MD, MS

Glenn J. Lesser, MD

\*W. Gregory Hundley, MD

\*Virginia Commonwealth University

1200 East Broad Street

P.O. Box 980335

Richmond, Virginia 23298

E-mail: [greg.hundley@vcuhealth.org](mailto:greg.hundley@vcuhealth.org)

Twitter: [@VCUHealthHeart](https://twitter.com/VCUHealthHeart), [@JenJordanPhD](https://twitter.com/JenJordanPhD)

<https://dx.doi.org/10.1016/j.jacc.2020.02.013>

© 2020 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please note: Funding for this study was provided by a National Institutes of Health, National Cancer Institute grant (1R01CA199167). The Wake Forest NCI Community Oncology Research Program and Eastern Cooperative Oncology Group-American College of Radiology Imaging Network support is provided by the National Institutes of Health, National Cancer Institute, program grants 5UG1CA189824 and 5UG1CA189828. Dr. Lesser has served as a consultant for Cancer Expert Now, Agios, and Stemline Therapeutics; and has received research funding from Vascular Biogenics, Incyte, and NewLink Genetics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. (UPBEAT [Understanding and Predicting Fatigue, Cardiovascular Decline, and Events After Breast Cancer]; [NCT02791518](https://clinicaltrials.gov/ct2/show/study/NCT02791518)). The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [JACC: CardioOncology author instructions page](#).

## REFERENCES

1. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst* 2012;104:1293-305.
2. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;25:3808-15.

- 3.** Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2010;55:2614-62.
- 4.** Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2\* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017;19:75.
- 5.** Forman DE, Fleg JL, Kitzman DW, et al. 6-Min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J Am Coll Cardiol* 2012; 60:2653-61.
- 6.** Scott JM, Haykowsky MJ, Eggebeen J, Morgan TM, Brubaker PH, Kitzman DW. Reliability of peak exercise testing in patients with heart failure with preserved ejection fraction. *Am J Cardiol* 2012;110:1809-13.
- 7.** Hicks KA, Hung J, Mahaffey KW, et al. Standardized definitions for end point events in cardiovascular trials; U.S. Food & Drug Administration, 2010.